
Case Studies

Q&A

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Alan Bennett (University of California, Davis): This question is for Ricke Kress on citrus greening. I recall in the National Academy report some discussion of delivering a resistance trait through rootstocks. Is that being explored in terms of delivery through a transgenic rootstock, for citrus or other woody species?

Ricke Kress: Yes. It is part of the industry-research effort. It's a determination to elucidate the relative importance of the scion or the rootstock or both.

Chris Wozniak (US Environmental Protection Agency): I have a question regarding some of the surveys a couple of you mentioned relative to people's perception of putting DNA back into the same species and whether you want to call it intragenics or cisgenics or Innate technology or whatever. Do you think that the people answering those questions really understand the difference as to whether you are plopping in an ORF or a new promoter? Do they really understand differences in, say, the amount of the trait that will be expressed in your version of the plant versus where you are getting the gene from?

Haven Baker: The answer is no.

Wozniak: That's pretty much what I figured.

Carter: We didn't try to differentiate between transgenic, cisgenic and intergenic.

Wozniak: I'm curious because in years of talking with people who are in this research—and reviewing grant proposals—everybody seems to tout their own version of what is cisgenic and what is intergenic and why theirs is better than the last guy's. One of the things that we have considered is that if you do manipulate control elements, promoter sequences, then you are dealing with a different scenario because then you are changing the tissue and expression pattern of that trait protein or whatever it is, as compared to, say, eating the same thing you have always been eating because the gene came from potato and it's in potato. Whereas when you do those manipulations it's not really the same, at least to some ways of thinking.

Baker: Scientific distinctions are usually lost on the general population. It's confusing if you use Google alerts of the reports of what you think the public perception is. Data generated by the International Food and Information Council is reasonably neutral—I hope—when they ask people, “Do you support biotech in your food?” They get answers similar to ours. Then you ask the next question, “Do you know if biotechnology is in your food?” and two thirds of Americans say they don't know and another 10% say no. So you are asking for opinions on subjects that consumers are largely uninformed of and probably want to stay that way as long as it's safe. So, yes, these distinctions get lost on the majority of the population, but 8% of people—it correlates highly with the organic crowd—are very against technology and very vocal. That's generally who we think about and who we hear about. It's a hard thing to get your arms around what people really think.

Audience Member: My question is again related to cisgenic and intragenic versus transgenic. When you are dealing with USDA-APHIS, FDA and so on, does that make your life easier?

Neal Carter: We never made the distinction. We just call it transgenic. The regulatory process essentially is the assessment of risk and the data package addresses that. If you can build a vector that is simpler, or do something that is going to require less data, than the regulatory process will be easier. But, at the end of the day, you have to address the risks.

Haven Baker: One more thing on why we did what we did. In the case of potatoes—and also tomatoes—you've already had market failures. Growers have long memories and so do industry participants. We talk about the Innate™ technology, partly to differentiate it from past efforts. That's not really geared toward the regulatory aspect. It's geared towards consumers, and, in our case, towards industry.

Roger Beachy (Global Institute for Food Security, Saskatoon): Two questions. We heard from oranges about \$3.2 to \$3.4 million for all the tests for regulatory approval of a new protein entry, and I didn't hear that in apples. I wonder if you would comment on the differences there and what does that reflect? Then I want John Purcell to address the issue of would you have done *Bt* sweet corn if you had to go through the whole process of deregulating the event rather than crossing it in?

Carter: From our perspective it's hard to define regulatory costs. I'm not sure what is meant by that. A lot of the costs—such as for field trials—you will incur anyway. I think I heard Dennis say a quarter of a million dollars—that kind of range—nothing like three or four or five million. But we haven't finished yet. Maybe we are going to see more costs.

Kress: We have looked at what we feel we have to do to work our way through the process identifying all the potential tests and data collection and so on that we have to put into our package. We are going to do what we have to do. I also have a board of directors that is very interested in what we are doing as well, so I need to give them some insight as to how this can work.

Carter: There's an important distinction, in that we are not going through the EPA. Also I'm not including the cost of the field trials and the 10 years of field data that we generated that we wanted to have ourselves. I'm thinking more of the incremental cost of putting those data together and doing the statistics on it in a way, shape and form that the regulatory people wanted to see it done. Maybe there's a few additional studies that we did, and then the sequencing of the events themselves. We hadn't fully sequenced them, we relied on Southern data and we went ahead and sequenced them—just some extra things we did for regulatory purposes.

Kress: In the scheme of economics, the regulatory package might be the cheapest part. When we start to build these trees and to commercialize them and move into the growth side of it, it's going to be expensive because with the new regulations on nursery operations, and so on, for every 100,000 trees in citrus right now it's about a million dollars to build a structure to meet all the requirements and handle it all. There are 60 million trees in the state of Florida, so there's a lot more to the puzzle.

Daniel Lineberger: There is a follow up question for John about sweet corn.

John Purcell: Let me provide a little context first. At Monsanto, as a scientist, you feel fortunate because there are significant investments in R&D, but there is also a stringent process for every project, and one of the milestones it hits is when it goes into the regulatory phase, because that's when you start assuming the regulatory costs. In each stage of the discovery process, we make priority decisions on which projects move forward. The challenge is in a lot of the vegetables. If you look at the number of markets in which we have to go for cultivation approvals alone. Look at tomatoes: It's a big market opportunity, but it's not like corn, cotton and soybean. It's a very distributive kind of market. It's \$500,000 to \$1 million at a time. So, when you look at those kinds of markets it's difficult to say whether you go a product-development route that will require the regulatory piece. Looking at that many cultivation approvals and then the import approvals for where those products are flowing, the numbers don't pencil out. Part of the stringency is what's called APV: at present value. When you look at the cost of developing the product and what will be the eventual return, and then the other piece that is in there is the risk

adjustment on that, which is what is the chance of getting all those approvals in order to have that commercialization. So a lot of these vegetable products from the transgenics just don't pencil out. The corn one—that's an interesting question. We started with the approval and so it wasn't a hard decision for us. I haven't done the numbers but I'd be skeptical. When you pencil it out could you justify it with the US market and then you look where else that corn would have to be produced if you didn't start with mon88 and mon89 which are already approved?

Peter Schuerman (Texas A&M Agrilife Research, College Station): The Arctic apple story is fascinating and it's particularly interesting that such a small company would take on that task. Your future plans include some protein traits. How will you finance those enterprises in the future?

Carter: We have to do this with Arctic to prove that we *can* do it. We have a grower group that I am part of that has always known that there is a lot of money in something that is new and different. With a GM apple, we aren't sure if that's still going to be the case because of the consumer push back. We have learned a lot regarding how to do it faster. We've learned how to negotiate the regulatory process. The science is actually relatively straightforward, and the great thing about it is that it works. We will chase the money, I guess, and apply for grants and leverage, we've been able to leverage our shareholder capital about 4 to 1 from a research point of view. It's very easy to fund the research. You don't get any leverage on the precommercialization component, which is the shark pit—the chasm you have to walk through that is very, very difficult. Dennis called it the Red Zone. The Red Zone for him included the regulatory piece. For us it's more the precommercialization phase, understanding the industry that you are working in, having an intimate idea of whom to talk with and how to sell it and maybe how to get a few key big companies involved to help steer that process. In fact, in all of the new traits we are working on, we have large tree-fruit-growing companies, usually vertically integrated, that are interested in that product and they will help partner in that cost.

Lineberger: So, they are investors?

Carter: They're not shareholders. It's fee-for-services-type work.

Schuerman: Venture capitalists?

Carter: Yes. These are people who got in early before they read the fine print: "Neal, what did you talk me into?" My wife and I are the two largest shareholders and so I guess we are just stupid or something. We have about 40 shareholders and half of them are fruit growers—people who are willing to speculate on being part of something new. I'm lucky. I'm involved in some other business activities and I dragged some of those guys in too, and maybe they aren't feeling so lucky, but I'm feeling lucky.

Purcell: With the portfolio process, it's rarely the technical feasibility that kicks things out on the vegetable side—insect control, virus control, those kinds of things we know we can do. Being with growers pretty much every day the value in there is there but when you think about how all the elements in the chain have to come together to do that, and then the international elements as I discussed, that's where it gets really problematic.

Tony Shelton (Cornell University, Ithaca): We've all heard about how great this technology is, but the main issue seems to be communication with the consumer. And I see, Neal, that you have a nice little friendly label, and people can go to your website and learn more about it. What happens if, all of a sudden, you have to slap a label on there that says "genetic engineered" and you don't not have control over the friendliness of the message. How will you deal with that?

Carter: If mandatory labeling laws come in with a skull and crossbones or something, sure it's not going to help. But identifying Arctics as Arctics with point-of-sale literature available—and these kinds of things—I don't think it will change much. I think that there is going to be fairly widespread understanding that this is a genetically engineered apple.

Shelton: And Rick, what about that for citrus? It's not going to apply to the fresh market, it's more for the juice.

Kress: No, it will be fresh as well. Although we are in Florida this is going to be a process that is going to have to go through the entire regulatory approval for the United States. It will affect all of citrus in all directions. From our perspective, we recognize the work that we are going to have, education-wise. With the various research that we have going, we are kind of in a horse race. We have several horses that have broken from the gate and as we go towards the third pole we will start to narrow that down and when we start looking towards the fourth, the finish line, that's when we will step out and become more involved in that overall education process because we will know the direction we are going. We can't work on an education process today with three different directions. That won't work. When we get to the direction we are going in and then we will move forward on education before we get commercial.

Christiane Deslauriers (Agriculture and Agrifood Canada, Ottawa): The objection that I hear most of the time from industry is the unpredictability of the regulatory system. The biggest impediment to progress in this kind of work is not knowing what the regulatory system is going to be. Given your experience, do you think it is realistic to ever think you will be able to know ahead of time—the question will be knowable ahead of time? And to what extent has that applied for each of you?

Kress: Part of our challenge has been that we are working with a tree. We are not working with a corn plant, potato or other annual. There is a gap in the information that the agencies have. The first time we went to DC and met with the agencies, we went with the

intent of asking a lot of questions and we were very open with what we were doing. So, we are working very closely with all three. I judge the quality of the meeting that we have when we are in DC by the number of questions that I come home with, and generally I come home with more questions than answers. That's okay, because that's what we have to do to get through this. That's how we are looking at it. We wish there were a template, but there isn't. We are going through step by step, and trying to be proactive.

Purcell: Roger Beachy talked about the inconsistency on the world stage and that's where we, a global seed company, see much unpredictability. Think about emerging and growth markets in Asia market where they might not even have a regulatory system in place. So you are developing your product while the regulatory system is being constructed and that's where a lot of the uncertainty comes in because you don't have harmonization. In many cases the rules are being written as people are trying to develop products and that, obviously, introduces a lot of uncertainty in when you can expect an approval or even what you have to do to put a submission together.

Carter: The smaller the company the bigger the uncertainty in terms of risk caused by regulatory timelines. You have a burn rate, but you don't know if it's going to take two years, three years, four years or five years. It's hard to know when you are going to get into the marketplace and start to see return on investments. In January 2012, we met with APHIS and FDA and a timeline was given. But, you leave the meeting and immediately there is slippage, and then they come out with their new timeline process and immediately there is more slippage. Such uncertainty builds risk and, typically, boards of directors and shareholders don't like risk. If you are trying to raise money they are going to say, "Yes, but what about the regulatory thing, where are you with that?" And you say, "Well I don't really know. We thought we would be done but we're not." These things are definitely impediments to raising capital.

Tom Redick (Global Environmental Ethics Counsel, Clayton): We've seen the labeling laws in Europe cost us literally billions in trade, measured by European economists who are very objective. The Connecticut labeling law has to include at least four states contiguous states. Assuming a bunch of states in the northeast enact a GM-labeling law, would that significantly impact your ability to go forward with your orange or apple or potato?

Kress: It's not going to slow us down because if we don't find a solution to this disease we're not going to have citrus. That's the bottom line there. Another thing, which, in a backhanded way, is in our favor, we won't be introducing tomorrow. We've got some years yet, still involved in this, so we are anticipating that this is all going to get sorted out. Again, a lot of companies that market orange juice are interested in how this will play out. On one hand we have time, and on the other hand we don't. It's all got to work.

Juan Landivar (Texas Agrilife Research, College Station): I think you said that you have until 2019 for deregulation. Where are we going to get our orange juice? From Brazil?

What is the plan? What is going to happen? Is there any way that the process can be accelerated?

Kress: I didn't go into all of our research. We have some other approaches that could provide interim solutions to shorten that timeline. One has to be optimistic. My board of directors asked me one time how we were addressing all of this and I said that I'm optimistic six out of seven days. They said, "What day aren't you?" And I said, "Well, that's the problem, I never know which day it's going to be."

Tom Turpen (Citrus Research and Development Foundation, Lake Alfred): For Neal—I thought it was brilliant—the selection of the trait and how it benefits the participants along the whole value chain. And also the communication of the technology—it was the best description of RNAi I've ever seen, with the railroad tracks. I wonder if you could preview for us the story you will use for the infectious-disease traits, because those will be adding a PIP. You did such a good job of communicating your Arctic apple story, how will you communicate your infectious-disease traits?

Carter: I don't quite have that story mapped out yet, so I can't answer your question, sorry. It would be premature at this stage. But, a couple of things—we go to see US Apple in Washington and they say, "Oh, if you had an agronomic trait, we would really like it because our growers would be behind it." And we respond, "Yeah, but consumers are the ones you have to please." So, we are really frustrated by the fact that every industry group we meet with—growers, grower/packers, shippers, their industry representative groups—they all want agronomic traits, and they are willing to support those and stand behind them and promote them and all the rest, so maybe we won't need to. We chose our trait because we felt that we needed to get the consumer on our side and that if we just jumped into scab or fire blight right off the start, we would be dead in the water. So they will be Arctic plus. They will be non-browning with fire blight resistance, non-browning with storage scald resistance—that sort of thing.

Lineberger: Just to put a little plug in here for Neal—if you go to his website there is a link to his TED talk on the integration of biotechnology. It's fascinating. He uses some very common-sense non-technical easy-to-understand approaches.